Medical Progress

Reye's Syndrome

DORIS A. TRAUNER, MD, *La Jolla, California*

Reye's syndrome (encephalopathy with fatty infiltration of the viscera) is an acute illness of childhood that produces hepatic dysfunction and metabolic encephalopathy. The disease is fatal in as many as 40% of cases. The cause is unknown. Several environmental agents, particularly salicylates and aflatoxin, have been implicated as possible toxins in this disorder. Treatment is directed at controlling intracranial pressure, reversing metabolic abnormalities and providing intensive supportive care. Normal neurologic function returns in most survivors.

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A great deal of publicity has surrounded recent information relating to Reye's syndrome. This disorder, which was first described in 1963 as a specific entity of encephalopathy with fatty infiltration of the viscera,[1] occurs most commonly in infants and children younger than age 17 years and only rarely in adults. The incidence is estimated at 0.31 cases per 100,000 children younger than 17 years,[2] though in at least one report there was an elevenfold higher incidence (3.5 cases per 100,000 children)[3] when milder, biopsy-proved cases are studied. Cases occur both sporadically and in "epidemics," the latter primarily following influenza outbreaks. Although cases occur throughout the year, there is some seasonal predilection, with late winter and early spring being "peak" times.[4]

Reye's syndrome has some interesting epidemiologic features for which there is no clear explanation. The disease tends to occur in white, middle-class children who live in suburban and rural areas.[4] The opposite appears to be true for infants younger than 1 year; these cases are more likely to occur in poor, inner-city dwellers and among members of ethnic minorities.[5]

Clinicopathologic Features

Reye's syndrome is a biphasic illness. The prodrome is a viral infection, with upper respiratory or gastrointestinal tract symptoms. Viruses most often associated with the disorder are influenza-B and varicella. Typically a child is recovering from this illness when the acute onset of recurrent vomiting develops, which progresses to encephalopathic symptoms (lethargy, agitation, delirium or coma) within 24 to 48 hours after vomiting begins. Seizures may occur at any time during the encephalopathic phase[6] but are more frequently seen in infants and younger children.[5] Respiratory abnormalities are common, with hyperventilation being most prominent. Apneic episodes may occur, particularly in infants.[5] The liver is often enlarged, but patients are anicteric. The disease may progress to deep coma with evidence of brain-stem dysfunction and occasionally is fatal (10% to 40% of cases).

Increased intracranial pressure is a common and severe complication.[7,8] Occasionally, acute pancreatitis may also complicate the clinical findings.

Results of laboratory investigations (Table 1) show evidence of liver dysfunction with elevated serum aminotransferases, hyperammonemia and a prolonged prothrombin time. The serum bilirubin value is normal. Hypoglycemia occurs in about 40% of patients and is encountered more frequently in children younger than 4 years.[6] Respiratory alkalosis is usually found, often with a concomitant metabolic acidosis. Creatine phosphokinase concentrations are elevated in serum.

Other laboratory abnormalities known to occur in Reye's syndrome include free fatty acidemia,[9] elevations in serum amino acid levels,[10] hyperuricemia and lactic acidemia.[6] Examination of the cerebrospinal fluid shows no abnormalities except for increased pressure and occasional hypoglycorrhachia in conjunction with hypoglycemia.

The most obvious pathologic abnormality by light microscopy is diffuse panlobular microvesicular fatty accumulation in the liver (Figure 1). Fatty infiltration may also be found in specimens from kidney, heart and skeletal muscle. Histochemical stains have revealed depletion of succinic acid dehydrogenase activity in the

From the Departments of Neurosciences and Pediatrics, University of California, San Diego, School of Medicine, La Jolla.
Reprint requests to Doris A. Trauner, MD, UCSD Medical Center (H-815), 225 Dickinson Street, San Diego, CA 92103.

TABLE 1.—*Hematologic and Metabolic Abnormalities in Cases of Reye's Syndrome*

↑ Leukocyte count
↑ Ammonia
↑ Serum aminotransferases
↑ Prothrombin time
↑ Creatine phosphokinase
↓ Serum and cerebrospinal fluid glucose
Respiratory alkalosis
Metabolic acidosis
↑ Serum short- and medium-chain fatty acids
↑ Amino acids (lysine, glutamine, alanine, α-amino-*N*-butyrate)
↑ Lactic acid
↑ Uric acid
↑ Blood urea nitrogen
↑ Amylase
↑ Cerebrospinal fluid glutamine
↓ Serum C1 and C1S complement activity

↑ = increased, ↓ = decreased

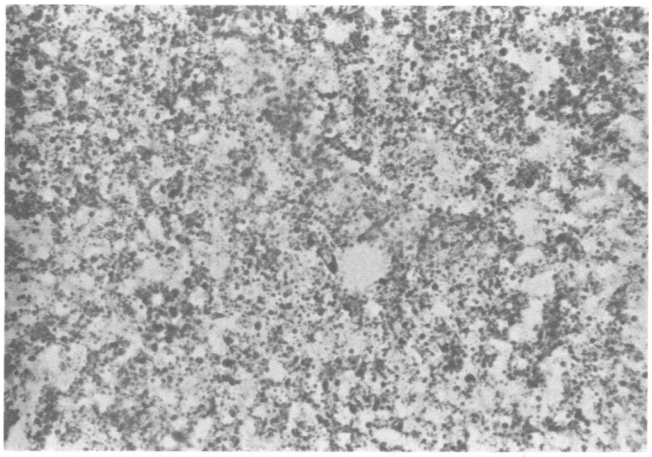

Figure 1.—Oil red O stain of liver biopsy specimen from patient with Reye's syndrome showing diffuse, microvesicular fatty infiltration. (Reduced from magnification × 600.)

liver.[11] Ultrastructural changes in liver mitochondria include swelling and pleomorphism, irregularity of the mitochondrial membrane and diminution of matrix granules.[12]

The principal neuropathologic change is the presence of diffuse cerebral edema. Changes due to anoxia may be observed. Brain mitochondrial abnormalities similar to those in the liver have been reported. The pancreas may have areas of focal necrosis, hemorrhage and inflammation.

Role of Salicylates and Other Toxins

The cause of Reye's syndrome is unknown. It is not the direct result of a viral infection such as encephalitis or hepatitis. Several hypotheses have arisen, including a viral toxin interaction, genetic predisposition and release of endogenous toxins. The possible role of aspirin in the etiology of Reye's syndrome has received much publicity in the past few years.

The possible involvement of salicylates was suggested as early as 1962, even before Reye's syndrome was recognized as a clinical entity. Mortimer and Lepow[13] reported four cases of infants with varicella infections who had received aspirin. In two of these clinical and pathologic features developed that were compatible with Reye's syndrome. In 1975 Linneman and co-workers[14] reviewed 56 patients with pathologically confirmed Reye's syndrome, 53 of whom had a history of salicylate ingestion. Two years later, Corey and associates[15] reported that 78% of 175 patients with Reye's syndrome had received aspirin and suggested a possible correlation. In recent studies from Arizona,[16] Ohio and Michigan,[17,18] case-control methods were used to study the possible relationship between salicylates and Reye's syndrome. Each study compared known cases of Reye's syndrome with control children of similar ages in whom viral illnesses developed similar to the prodrome of the children with Reye's syndrome. None of the control children were admitted to hospital for their illness. The studies used questionnaires answered by the parents after the illnesses were identified. Parents were interviewed anywhere from two days to six weeks after the onset of the illness in both patients and controls. In all of the studies, patients with Reye's syndrome had taken salicylate-containing medications during the prodromal illness much more frequently than control children, even when the two groups were matched for fever, and Reye's syndrome patients took more salicylates than non-Reye's syndrome controls who had taken salicylates. These findings suggested a possible causal relationship between salicylate ingestion during the prodromal illness and the subsequent development of Reye's syndrome.

These reports have led to a great deal of discussion about the safety of administering aspirin in viral illnesses. There are several difficulties with this type of study. There may be "recall bias," in which parents of more severely ill children tend to remember details of the illness more accurately than parents of less severely ill children. Also, parents whose children are more severely ill may try more medications to treat that illness and this may explain the more frequent use of salicylates in the Reye's syndrome group. There may be mismatching of the severity of the prodromal illness in Reye's syndrome versus control children. For example, many more of the children in whom Reye's syndrome developed had fever during their prodrome than did the control children.

After reviewing the data, including arguments regarding the limitations of the case-control method, the Committee on Infectious Disease of the American Academy of Pediatrics concluded that, despite potential pitfalls in the study, there was a "high probability that the administration of aspirin contributes to the causation of Reye's syndrome" and that aspirin "should not be prescribed under usual circumstances for children with varicella or those suspected of having influenza."[19]

In addition to the case-control studies, there are other data that suggest at least a possible relationship between salicylates and Reye's syndrome. Clinically, there are many similarities between Reye's syndrome and salicylate toxicity. These include encephalopathy, hyperven-

tilation, abnormalities in liver function, metabolic acidosis, respiratory alkalosis and occasionally fatty changes in the liver. In experimental animals, salicylates are known to uncouple oxidative phosphorylation[20] and may, thus, impair energy metabolism. It is conceivable, therefore, that salicylates may potentiate the adverse effects of certain viruses on mitochondrial function and in this way lead to the development of Reye's syndrome.

Salicylates are not the only answer, however. Many children with Reye's syndrome have not taken any salicylate-containing compound. Also, this would not explain why millions of children take aspirin for viral illnesses and Reye's syndrome never develops.

A Reye's-like illness in Thailand is known to be caused by aflatoxin, a metabolite of the fungus *Aspergillus flavus*.[21] Aflatoxin is found in corn and peanut products. In several reports in the United States, aflatoxin was found in blood or tissue specimens of patients with Reye's syndrome.[22,23] Other investigators have been unable to find any association of aflatoxin, however. Jamaican vomiting sickness has symptoms similar to those of Reye's syndrome and is caused by ingesting hypoglycin A, a compound found in unripe akee fruit.[24] In experimental animals, a Reye's-like syndrome can be produced by administering 4-pentenoic acid, a derivative of hypoglycin A.[25] Another experimental model has been devised using a combination of virus infection and insecticide applied to the animal.[26] Thus, there appears to be more than one environmental toxin that can produce symptoms of Reye's syndrome.

There are other etiologic considerations as well. Thaler[27] has suggested a possible genetic predisposition or inborn error of metabolism as the underlying factor in the development of Reye's syndrome. Some of the urea-cycle disorders, as well as systemic carnitine deficiency, can resemble Reye's syndrome. Finally, endogenous toxins may be liberated during a viral illness that could result in encephalopathy and other changes of Reye's syndrome. Short- and medium-chain fatty acids are elevated in the serum of patients with Reye's syndrome.[9] These compounds, when injected into experimental animals, reproduce the major clinical, pathologic and biochemical features of Reye's syndrome.[28,29] It has recently been shown that experimental influenza B infection in mice results in a block in mitochondrial β-oxidation of fatty acids with subsequent elevations in serum free fatty acid concentrations.[30] A mechanism such as this may be responsible for the development of the symptoms of Reye's syndrome. Ammonia has intermittently been implicated as the endogenous toxin possibly responsible for hepatic encephalopathy and Reye's syndrome. Several investigators have found an association between serum ammonia concentrations and the severity of the disease.[31,32] In experimental animals injected with high concentrations of ammonia-containing salts coma developed, though the serum concentrations of ammonia that are required to produce coma in experimental animals far exceed the usual degree of hyperammonemia in children with Reye's syndrome.[33]

In summary, more than one etiologic factor are likely responsible for the development of the symptom complex known as Reye's syndrome. Until there is more specific knowledge about the pathogenesis of this disorder, however, it would seem prudent to try other means of reducing fever and discomfort in children with viral illnesses and, in particular, flulike illnesses and varicella, before resorting to salicylate treatment.

Treatment

Most treatment protocols cover three general areas: intensive supportive care, correction of metabolic abnormalities and treatment of increased intracranial pressure. Because the etiology of the disorder has not been determined, no specific therapeutic approach has been identified.

Any child suspected of having Reye's syndrome, even in the early stages, should be admitted to a pediatric intensive care unit for careful observation. Evaluation of a child with Reye's syndrome involves assigning an appropriate stage to the disease. Children with stage 1 disease are lethargic but able to follow verbal commands, have purposeful responses to pain and evidence of hepatic dysfunction. Stage 5 is the most severe, and in this case the child is in coma with flaccid muscle tone, no response to pain, no oculocephalic reflexes and pupils may be unresponsive to light. For stages 1 and 2, patients are generally treated with intravenous administration of hypertonic glucose solutions, are monitored frequently for respiratory or blood pressure changes and observed closely.[3] For stages 3 through 5, a variety of treatment protocols exist. In our center, the following is used.[34] Nasotracheal tubes are electively inserted and arterial and central venous pressure lines, as well as nasogastric tubes and Foley catheters. Mechanical ventilation is used and patients are paralyzed with a neuromuscular blocking agent such as pancuronium bromide. Controlled hyperventilation is often used in an effort to decrease intracranial pressure. Cooling mattresses are used to keep body temperatures at normal range. Hypertonic glucose solutions given intravenously, as well as insulin, are often used.

Agents to reduce serum ammonia concentrations are also often used, the most common being neomycin sulfate or lactulose. The prothrombin time and other coagulation abnormalities may be corrected by administration of fresh frozen plasma. Exchange transfusion is used in some centers to correct various metabolic and hematologic abnormalities.

Intracranial pressure elevations are treated by administering osmotic diuretics, including mannitol, other agents such as glycerol or furosemide and controlling hyperventilation and muscular paralysis. Intracranial pressure is usually monitored by using intraventricular, subarachnoid or epidural monitors.

The role of high-dose barbiturates in the treatment of intracranial pressure elevations in Reye's syndrome[35] is somewhat controversial. Such therapy is effective in

reducing increased intracranial pressure, but may complicate the clinical course and slow the recovery.[36] Thus far, there is no convincing evidence that the outcome is improved substantially by the use of high-dose barbiturates.

Conclusions

Reye's syndrome is an acute, severe, metabolic encephalopathy occurring primarily in infants and children. The pathogenesis of the disorder is unknown, although a variety of environmental toxins have been implicated. Treatment is primarily supportive. However, with more aggressive therapeutic regimens that have been developed over the past ten years, the prognosis has improved considerably. Early reports[1] indicated a mortality of 80% to 90% in most series. Current mortality ranges between 10% and 40%.[4,34] Whether this is the result of more aggressive treatment, earlier diagnosis of the disease or the recognition of many milder cases is not clear. For whatever reason, many more patients survive the acute illness. For most of those children, the outcome is good.[37] They may return to completely normal function with no significant long-term neurologic disabilities. Early diagnosis and appropriate supportive therapy appear to be important in halting the progress of the disease and insuring a better outcome for these children.

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